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08/17/00 JC810 U.S. PTO

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 41145-1001

005179

PATENT TRADEMARK OFFICE

08/17/00 jc764 U.S. PTO 09/642236

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN

and invented by:

GEORGE R. SCHWARTZ

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☒ **Continuation-in-part (CIP)** of prior application No.: **09/ filed 6/5/00**

Which is a:

☐ **Continuation** ☐ **Divisional** ☒ **Continuation-in-part (CIP)** of prior application No.: **09/499,198**

Which is a:

☒ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: **60/150,040**

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having **18** pages and including the following:
   - a. ☒ Descriptive Title of the Invention
   - b. ☒ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Microfiche Appendix *(if applicable)*
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☐ Brief Description of the Drawings *(if drawings filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 41145-1001
Total Pages in this Submission

Application Elements (Continued)

3. ☐ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☐ Formal b. ☐ Informal Number of Sheets _____

4. ☒ Oath or Declaration
   a. ☒ Newly executed *(original or copy)* ☐ Unexecuted
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☒ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Computer Program in Microfiche

7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*
   a. ☐ Paper Copy
   b. ☐ Computer Readable Copy
   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*

9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*

10. ☐ English Translation Document *(if applicable)*

11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☒ Acknowledgment postcard

14. ☒ Certificate of Mailing
    ☐ First Class ☒ Express Mail *(Specify Label No.):* **EL548785045US**

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 41145-1001
Total Pages in this Submission

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☒ Small Entity Statement(s) - Specify Number of Statements Submitted: 1

17. ☒ Additional Enclosures *(please identify below):*

Associate Power of Attorney

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	32	- 20 =	12	x $9.00	$108.00
Indep. Claims	3	- 3 =	0	x $39.00	$0.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$345.00
OTHER FEE *(specify purpose)*					$0.00
				TOTAL FILING FEE	$453.00

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☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **13-4213** as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: **August 17, 2000**

Signature

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CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **GEORGE R. SCHWARTZ**	Docket No. **41145-1001**

Serial No.	Filing Date	Examiner	Group Art Unit
To Be Assigned	**Herewith**	**To Be Assigned**	**To Be Assigned**

Invention: **INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN**

I hereby certify that this **CONTINUATION-IN-PART APPLICATION**
(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Commissioner of Patents and Trademarks, Washington, D.C. 20231-0001 on **AUGUST 17, 2000**
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Practitioner's Docket No.41145-1001 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☒ Applicant: **GEORGE R. SCHWARTZ** ☐ Patentee _____

☐ Application No. ☐ Patent No. _____

☐ Filed on ☐ Issued on _____

Title: **INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN**

STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(b)) - INDEPENDENT INVENTOR

As a below named inventor, I hereby state that I qualify as an independent inventor, as defined in 37 CFR 1.9(c), for purposes of paying reduced fees to the United States Patent and Trademark Office under Sections 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office, with regard to the invention described in

☒ the specification filed herewith, with title as listed above.

☐ the application identified above.

☐ the patent identified above.

I have not assigned, granted, conveyed or licensed, and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CRR 1.9(c), if that person had made the invention, or to any concern that would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

☒ No such person, concern, or organization exists.

☐ Each such person, concern or organization is listed below. *

**NOTE: Separate statements are required from each named person, concern or organization having rights to the invention as to their status as small entities. (37 CFR 1.27)*

FULL NAME _____

ADDRESS _____

_____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

(check the following item, if desired)

NOTE: The following verification statement need not be made in accordance with the rules published on Oct. 10, 1997, 62 Fed. Reg. 52131, effective Dec. 1, 1997.

NOTE: "The presentation to the Office (whether by signing, filing, submitting, or later advocating) of any paper by a party, whether a practitioner or non-practitioner, constitutes a certification under § 10.18(b) of this chapter. Violations of § 10.18(b)(2) of this chapter by a party, whether a practitioner or non-practitioner, may result in the imposition of sanctions under § 10.18(c) of this chapter. Any practitioner violating § 10.18(b) may also be subject to disciplinary action. See § § 10.18(d) and 10.23(c)(15)." 37 CFR § 1.4(d)(2).

☒ I hereby certify that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

GEORGE R. SCHWARTZ
Name of Inventor

George R Schwartz
Signature of Inventor

Date 17 August 2000

Name of Inventor

Signature of Inventor

Date

Name of Inventor

Signature of Inventor

Date

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PATENT APPLICATION

INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN

BACKGROUND OF THE INVENTION

This application is a continuation-in-part application of U.S. Patent Application Serial No. 09/_____, entitled "Method of Enhancement of Neurologic Recovery in Human Nervous System Damage by Use of Pharmaceutical Thrombopoietin", to George R. Schwartz, filed on June 5, 2000, which in turn is a continuation-in-part of U.S. Patent Application Serial No. 09/499,198, entitled "Method of Enhancement of Neurologic Recovery in Human Nervous System Damage by Use of Pharmaceutical Thrombopoietin," to George R. Schwartz, filed February 7, 2000, now abandoned, and which claimed the benefit of U.S. Provisional Application Serial No. 60/150,040 , entitled "Method of Enhancement of Neurologic Recovery in Human Nervous System Damage by Use of Pharmaceutical Thrombopoietin", to George R. Schwartz, filed August 20, 1999. The specification of each of the foregoing is incorporated herein by reference.

Field of the Invention (Technical Field):

This invention relates to treatment of human neurologic damage, and in particular to a method for increased regeneration and repair of damaged neurons and nerve axon myelin coatings, and nerve cell repair.

DESCRIPTION OF THE PREFERRED EMBODIMENTS
(BEST MODES FOR CARRYING OUT THE INVENTION)

Demyelination occurs when the myelin coating around nerve axons degenerates resulting in a defect in the ability to transmit nerve impulses. For example, multiple sclerosis is a disease of unknown cause in which degeneration occurs in the myelin sheath surrounding the nerves. This demyelination is also found in many other diseases such as transverse myelitis. Demyelination also occurs after trauma to the brain or spinal cord, after a stroke, in neurodegenerative diseases such as amyotropic lateral sclerosis and Alzheimer's disease, as well as in viral diseases including AIDS.

A cell type in the nervous system called the oligodendroglia is intimately involved in myelin regeneration, repair and maintenance of the nerve cells. Repair occurs by the repetitive wrapping of the plasma membranes of the oligodendroglia cells around damaged nerve cells and offers continuing metabolic nerve cell support. In the art, it has been established that for 0-2A progenitor cells that produce oligodendroglia cells proliferation is induced in culture by type-1 astrocytes. A recognized mitogen for 0-2A progenitor cells is platelet-derived growth factor (PDGF), and PDGF is a potent mitogen for 0-2A progenitor cells in vitro. Thus, laboratory experimentation has suggested that PDGF is crucial for the control of nerve cell repair and myelination in the nervous system.

It is also known in the art that the development of oligodendrocytes from precursor cells also includes an effector component which depends on thyroid hormone that stops cell division and initiates differentiation at the appropriate time.

Further, it is also known in the art that proteins generally referred to as thrombopoietins support biological activity that ultimately results in the production of platelets and other cells from the myeloid line, including markedly increasing PDGF production. Methods of preparation of thrombopoietin are disclosed in recent patents, for example, U.S. 5,795,569 issued to Amgen, Inc. and processes for producing them by recombinant genetic engineering techniques are also disclosed. Hence, the

availability of thrombopoietins in pharmaceutically available quantities is to be expected in the near future.

SUMMARY OF THE INVENTION

A method of treatment of degenerative neurologic diseases provides for the administration of therapeutically effective amounts of an enhancement agent, such as thrombopoietin, to enhance the regeneration of neuron cells. A regulatory agent, such as thyroid hormone or thyrotropin, may also be included as a regulator of cell division and differentiation. The method may be used with humans and also with other mammals with neurologic damage.

The thrombopoietin may be orally ingested by the patient, or may be administered by intravenous, intramuscular or intrathecal injection.

The method can further include the step of administering thyroid hormone to the patient. The thyroid hormone may be orally ingested by the patient, or may be administered by intravenous, intramuscular or intrathecal injection. The thyroid hormone may include thyroid hormone extract or synthetic thyroid hormone.

The method can also further include the step of stimulating human thyroid production by administering thyrotropin to the patient. The thyrotropin may be orally ingested by the patient, or may be administered by intravenous, intramuscular or intrathecal injection.

The thrombopoietin may be isolated from a mammal, made by recombinant means, or made by synthetic means. It may be human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin. The therapeutically effective amount of thrombopoietin ranges from about 1.0 to about 100 µg/kg body weight per day.

In the method of this invention, the thyroid hormone can be co-administered to the patient with the thrombopoietin. In an alternative method, the thyrotropin can be co-administered to the patient with the thrombopoietin.

The invention further consists of a pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyroid hormone. The composition can contain between about 0.07 to about 10 mg of thrombopoietin per dose unit. The composition may be formulated such that it contains between about one and about three times as much thyroid hormone as thrombopoietin. In this composition, the thrombopoietin may be isolated from a mammal, made by recombinant means, or made by synthetic means. The thrombopoietin may be human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin. The thyroid hormone may be thyroid hormone extract or synthetic thyroid hormone.

The invention further consists of a pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyrotropin. The composition can contain between about 0.07 to about 800 mg of thrombopoietin per dose unit. In this composition, the thrombopoietin may be isolated from a mammal, made by recombinant means, or made by synthetic means. The thrombopoietin may be human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin.

A primary object of the present invention is to provide a method and formulation for neuron or myelin regeneration and maintenance in the nervous system.

Another object of the present invention is to provide a method for neuron and myelin regeneration and maintenance using endogenous platelet-derived growth factor (PDGF), production of which is induced by use of an enhancement agent.

Another object of the present invention is to increase PDGF production by administration of a therapeutically effective amount of thrombopoietin (TPO).

Another object of the invention is to provide a regulatory agent which effects a decrease in the rate of cellular division of oligodendrocytes and initiates differentiation into functional neuronal support cells.

Another object of the invention is to provide a method for treatment of neurological disorders including administration of TPO and co-administration or sequential administration of a regulatory agent, such as thyroid hormone, thyrotropin or the like.

Other objects, advantages and novel features, and further scope of applicability of the present invention will be set forth in part in the detailed description to follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS
(BEST MODES FOR CARRYING OUT THE INVENTION)

The present invention discloses a method of treatment of peripheral and central neurological diseases by the administration to patients of an enhancement agent in appropriate form and quantity. The treatment is disclosed for nervous system disorders, including diseases such as transverse myelitis, multiple sclerosis, demyelination occurring after trauma to the brain or spinal cord, as well as stroke, degenerative diseases such as Alzheimer's and amyotrophic lateral sclerosis, and viral diseases such as AIDS, as well as peripheral nerve injury. The enhancement agent serves to stimulate the production of

oligodendroglia and other glial cells in the repair of damaged neurons and nerve axons incident to such diseases.

The enhancement agent may be thrombopoietin which may be administered as a liquid or solid in the form of oral tablets, intravenous injection, intrathecal injection or intramuscular injection, depending upon the course of therapy followed.

In a second embodiment of the invention, a regulatory agent is used, which may be thyroid hormone in the form of thyroid extract, stimulation of human production by thryrotropin (thyroid-stimulating hormone), or synthetic thyroid hormone combined with the enhancement agent therapy to regulate cell division and oligodendroglia production.

Prior to describing the present invention in detail, the following definitions are given:

Enhancement agent: Includes any substance which, when administered to a mammal, results in the direct or indirect production of platelet-derived growth factor (PDGF). Examples of enhancement agents include thrombopoietin (TPO) and other mpl ligands, variants and derivatives thereof, and the like.

Thrombopoietin: Includes TPO produced by any means, including TPO isolated from a mammal, made by recombinant means and made by synthetic means. TPO may be human TPO, a fragment of human TPO, a variant polypeptide of TPO, a chimeric polypeptide of any of the foregoing and the like. The TPO may further be modified, and may be pegylated, glycosolated and the like. The TPO may further be present in a formulation including one or more carriers or excipients. Various forms and formulations of TPO are described in, among others, U.S. Patent Nos. 5,795,569; 5,879,673; and 5,989,537.

Regulatory agent: Includes any substance which, when administered to a mammal, results in the direct or indirect alteration of cell division rates and induction of differentiation, specifically of oligodendrocyte cells. Regulatory agents include thyroid hormone, thyrotropin and the like. The effort of these regulatory agents are described generally in Rodriguez-Pena A: Oligodendrocyte development and thyroid hormone. *J. Neurobiol* 1999, Sep. 15;40(4):497-512; Ahlgren SC, Wallace H, Bishop J, Neophytou C, Raff MC: Effects of thyroid hormone on embryonic oligodendrocyte precursor cell development in vivo and in vitro. *Mol Cell Neurosci* 1997;9(5/6);420-32; Gao FB, Apperly J, Raff M: Cell-intrinsic timers and thyroid hormone regulate the probability of cell-cycle withdrawal and differentiation of oligodendrocyte precursor cells. *Dev Biol* 1998 May 1;197(1):54-66; Ahlgren SC, Wallace H, Bishop J, Neophytou C, Raff MC: Effects of thyroid hormone on embryonic oligodendrocyte precursor cell development in vivo and in vitro. *Mol Cell Neurosci* 1997;9(5/6);420-32; and Durand B, Raff M: A cell-intrinsic timer that operates during oligodendrocyte development. Bioessays 2000 Jan; 22(1):64-71. The thyroid hormone, thyrotropin or the like may be isolated from a mammal, made by synthetic means, made by recombinant means, or made by any means known in the art. The regulatory agent may further be present in a formulation including one or more carriers or excipients.

The methods and substances of this invention may be used in the treatment of any of a variety of conditions resulting in neurological damage, including peripheral and central nervous system (CNS) injury, disease or disorders. CNS disorders encompass numerous afflictions such as neurodegenerative diseases (e.g. Alzheimer's and Parkinson's), acute brain injury (e.g. stroke, head injury, cerebral palsy) and a large number of CNS dysfunctions (e.g. depression, epilepsy, schizophrenia). In recent years neurodegenerative disease has become an important concern due to the expanding elderly population which is at greatest risk for these disorders. These diseases include Alzheimer's disease, multiple sclerosis (MS), Huntington's disease, amyotrophic lateral sclerosis, and Parkinson's disease. CNS disorders also encompass CNS trauma, such as results from stroke, epilepsy, traumatic injury and the like. Further, many viral diseases, including AIDS, result in CNS disorders.

The enhancement agent may be formulated as set forth above, and administered by any art conventional means. In the case of TPO, a therapeutically effective amount is administered, resulting in PDGF expression. Relatively low dosages may be employed, from about 1.0 to about 100 µg/kg body weight of the patient, and preferably about 5 to about 10 µg/kg body weight.

The TPO can be administered through various routes including via the nose or lung, cutaneously, subcutaneously, intrathecally, and preferably intravenously. Depending upon the route of administration, the TPO is preferably administered in combination with an appropriate pharmaceutically acceptable carrier or excipient. When administered systemically, the therapeutic composition should be pyrogen-free and in a parenterally acceptable solution. These conditions are generally well known and accepted to those of skill in the appropriate art.

Briefly, dosage formulations of the materials of the present invention are prepared for storage or administration by mixing the compound having the desired degree of purity with physiologically acceptable carriers, excipients and/or stabilizers. Such materials may include buffers such as phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight peptides such as polyarginine, proteins such as serum albumen, gelatin or immunogloulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid or arginine; monosaccharides, disaccharides and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins; chelating agents such as EDTA; sugar alcohol such as mannitol or sorbitol; counter-ions such as sodium and/or non-ionic surfactants such as Tween, Pluronics or polyethylineglycol. The TPO may be administered as the free acid or base form or as a pharmaceutically acceptable salt.

The TPO may be administered in sustained-release formulations, including polymeric substrates, hydrogels, liposomes and the like.

The regulatory agent may similarly be formulated as set forth above, and administered by any art conventional means. In the case of thyroid hormone, therapeutically effective amounts may be employed, resulting in a decrease in cellular division of oligodendrocytes and further differentiation into functional neuronal repair cells.

Any of a variety of thyroid hormones may be employed as a regulatory agent, including but not limited to purified thyroid, levothyroxine, liothyronine, and thyroglobulin. These are available in oral tablet formulations, and in the case of levothyroxine, additionally as an injectable parenteral. In usual oral dosage forms, from about 0.10 to 0.125 mg per day of levothyroxine is administered, for liothyronine sodium from about 25 to 50 µg per day is administered, for thyroglobulin from about 32 to 160 µg per day is administered, and for dessicated thyroid from about 15 to 120 mg per day is administered. Combinations of the foregoing may also be administered, such as liotrix, a combination of levothyroxine and liothyronine. Injectable levothyroxine, from about 50 to 200 µg per day, may be injected into a muscle or into a vein.

Thyrotropin, also called thyroid-stimulating hormone, may alternatively be employed to increase endogenous thyroid production. Thyrotropin is available as an injectable parenteral. Thyrotropin may be produced by any means known in the art, including as a recombinant form of human thyroid-stimulating hormone. Sufficient thyrotropin is administered to increase thyroid levels to that desired, with monitoring as required by any of a variety of available thyroid assays.

In one embodiment, a patient with a CNS disorder is administered from about 1 to 50 µg/kg body weight of TPO by intravenous injection, with such injections occurring every 2 days for a period of at least 8 days. At a suitable time, such as 10 days after the initial injection of TPO, administration of thyroid hormone is initiated. The thyroid hormone administration, for example a Synthroid® preparation (levothyroxine), is at a rate of about 2 to 4 µg/kg body weight per day, and is continued for a suitable period, such as 21 days.

Multiple courses of therapy may be undertaken, such that TPO and thyroid hormone administration are alternated. There may also be periods of time between courses of therapy in which periods may be fixed or may be related to the onset of symptoms of CNS disorder.

The enhancement agent and regulatory agent may be co-administered, as part of a single formulation. Thus, a treatment regimen may be employed in which both TPO and thyroid hormone are co-administered. Alternatively, TPO may be initially administered without thyroid hormone and after a suitable period administration of a formulation including TPO and thyroid hormone or thyrotropin is initiated.

The invention is further illustrated by the following non-limiting examples.

Example 1

B6SJL-TgN(SOD1-G93A)1Gur strain mice were obtained from The Jackson Laboratory, Bar Harbor, ME. The transgene in these mice carries a high copy number of a mutant allele human SOD1 containing the Gly93 -->Ala (G93A) substitution (often referred to as G1H). Mice progressively become paralyzed in one or more limbs, with paralysis due to loss of motor neurons from the spinal cord. The mice are generally described in Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, Chen W, Zhai P, Sufit RL, Siddique T: Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. *Science* 264:1772-1775 (1994), and use of these mice as a model of familial amyotrophic lateral sclerosis is described in Chiu AY, Zhai P, Dal Canto MC, Peters TM, Kwon YW, Prattis SM, Gurney ME: Age-dependent penetrance of disease in a transgenic mouse model of familial amyotrophic lateral sclerosis. *Mol Cell Neurosci* 6:349-362 (1995).

At 105 days following birth, mouse A began manifesting objective symptoms of limb paralysis. A protocol as described in **Table 1** was followed.

Table 1	
Days Following Birth	**Administration**
107	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
110	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
113	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
117	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin and 0.25 cc i.p. of a solution containing 500 µg/cc of thyrotropin releasing hormone
119	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
121	Synthroid®, 0.1 mg in 2 ounces of drinking water, ad libitum

The thrombopoietin was obtained from Rand D. Systems, Inc. (Minneapolis, MN) as carrier-free recombinant thrombopoietin and the thryrotropin was obtained from Ferring Pharmaceuticals; both were administered by intraperitoneal (i.p.) injection. Synthroid®, a form of levothyroxine, was obtained from Flint Pharmaceuticals in 100 µg tablets.

At day 111, marked improvement was observed, with elimination of shaking and limpness and improved muscle tone. At day 113, shaking resumed with observed early weakness developing. By day 115 marked hind limb weakness was observed. By day 118, decreased weakness was observed, although paresis remained in the left hind quarters. On day 120, increased mobility was observed. On day 122, marked improvement in front limbs was observed. Recurrence and increasing front limb weakness was observed on day 124. The mouse died at day 126.

Example 2

A litter mate of mouse A, referred to as mouse B, was administered a protocol as described in **Table 2**, with administration commencing prior to the onset of any objective symptoms.

Table 2	
Days Following Birth	**Administration**
87	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
91	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
93	0.6 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
95	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
105	Synthroid®, 0.1 mg in 4 ounces of drinking water, ad libitum through remaining life
126	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin

With this protocol, no objective signs were observed until day 121, when slight posterior weakness was noted. This was 16 days following onset of objective signs of illness in the litter mate mouse A. At day 129, posterior limb paralysis was observed, with the fore limbs remaining functional but some weakness observed in the left front. The mouse died on day 132.

Example 3

A B6SJL-TgN(SOD1-G93A)1Gur strain mouse as described in Example 1 was obtained, referred to as mouse C. Mouse C was administered a protocol as described in **Table 3**, with administration commencing prior to the onset of any objective symptoms.

Table 2	
Days Following Birth	**Administration**
80	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
84	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
86	0.6 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
88	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
92	Synthroid®, 0.1 mg in 4 ounces of drinking water, ad libitum through remaining life

With this protocol, no objective signs of illness were observed through day 110, more than two standard deviations from the expected onset of sickness (91 ± 14 days).

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Although the invention has been described in detail with particular reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of the present invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all references, applications, patents, and publications cited above are hereby incorporated by reference.

CLAIMS

What is claimed is:

1. A method of treatment of neurologic damage in a mammal, comprising the step of administering therapeutically effective amounts of thrombopoietin to the mammal.

2. The method of claim 1 wherein the step of administering the thrombopoietin comprises orally ingesting the thrombopoietin.

3. The method of claim 1 wherein the step of administering the thrombopoietin comprises intravenously injecting said thrombopoietin.

4. The method of claim 1 wherein the step of administering said thrombopoietin comprises intramuscularly injecting said thrombopoietin.

5. The method of claim 1 wherein the step of administering the thrombopoietin comprises intrathecally injecting the thrombopoietin.

6. The method of claim 1 further comprising the step of administering thyroid hormone to the mammal.

7. The method of claim 6 wherein said step of administering the thyroid hormone comprises orally ingesting the thyroid hormone.

8. The method of claim 6 wherein said step of administering the thyroid hormone comprises intravenously injecting the thyroid hormone.

9. The method of claim 6 wherein the step of administering said thyroid hormone comprises intramuscularly injecting the thyroid hormone.

10. The method of claim 6 wherein the step of administering the thyroid hormone comprises intrathecally injecting the thyroid hormone.

11. The method of claim 6 wherein the step of administering the thyroid hormone comprises administering thyroid hormone extract.

12. The method of claim 6 wherein the step of administering the thyroid hormone comprises administering synthetic thyroid hormone.

13. The method of claim 1 further including the step of stimulating human thyroid production by administering thyrotropin.

14. The method of claim 13 wherein the step of administering the thyrotropin comprises orally ingesting the thyrotropin.

15. The method of claim 13 wherein the step of administering the thyrotropin comprises intravenously injecting the thyrotropin.

16. The method of claim 13 wherein the step of administering the thyrotropin comprises intramuscularly injecting the thyrotropin.

17. The method of claim 13 wherein the step of administering the thyrotropin comprises intrathecally injecting the thyrotropin.

18. The method of claim 1 wherein the thrombopoietin is selected from the group consisting of a thrombopoietin isolated from a mammal, a thrombopoietin made by recombinant means, and a thrombopoietin made by synthetic means.

19. The method of claim 1 wherein said thrombopoietin is selected from the group consisting of human thrombopoietin, a fragment of human thrombopoietin, and a variant polypeptide of human thrombopoietin.

20. The method of claim 1 wherein the therapeutically effective amount ranges from about 1.0 to about 100 µg/kg body weight per day.

21. The method of claim 6 wherein the thyroid hormone is co-administered to the mammal with the thrombopoietin.

22. The method of claim 13 wherein the thyrotropin is co-administered to the mammal with the thrombopoietin.

23. A pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyroid hormone.

24. The composition of claim 23, comprising between about 0.07 to about 10 mg of thrombopoietin per dose unit.

25. The composition of claim 23 wherein the composition contains between about one and about three times the usual dose for thyroid hormone as for thrombopoietin.

26. The composition of claim 23 wherein the thrombopoietin is selected from the group consisting of a thrombopoietin isolated from a mammal, a thrombopoietin made by recombinant means, and a thrombopoietin made by synthetic means.

27. The composition of claim 23 wherein the thrombopoietin is selected from the group consisting of human thrombopoietin, a fragment of human thrombopoietin, and a variant polypeptide of human thrombopoietin.

28. The composition of claim 23 wherein the thyroid hormone is selected from the group consisting of thyroid hormone extract and synthetic thyroid hormone.

29. A pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyrotropin.

30. The composition of claim 29, comprising between about 0.07 to about 10 mg of thrombopoietin per dose unit.

31. The composition of claim 29 wherein the thrombopoietin is selected from the group consisting of a thrombopoietin isolated from a mammal, a thrombopoietin made by recombinant means, and a thrombopoietin made by synthetic means.

32. The composition of claim 29 wherein the thrombopoietin is selected from the group consisting of human thrombopoietin, a fragment of human thrombopoietin, and a variant polypeptide of human thrombopoietin.

INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN

ABSTRACT OF THE DISCLOSURE

A method of treatment of and composition for human degenerative neurologic diseases discloses the administration of therapeutically amounts of an enhancement agent, such as thrombopoietin, to enhance the repair of neurons, including re-myelinization. A regulatory agent, such as thyroid hormone or thyrotropin, may also be included as part of the method and composition as a regulator of cell division and oligodendroglia production.

Docket No.
41145-1001

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/150,040	August 20, 1999
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

09/499,198	February 7, 2000	Abandoned
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
09/	June 5, 2000	Pending
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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PATENT APPLICATION

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 via EL548785045US on the date indicated below, addressed to the Box Design, Commissioner for Patents, Washington, D.C. 20231.

Stacy E. Jenkins — 8/17/00

Stacy E. Jenkins, Paralegal — Date Signed

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	GEORGE R. SCHWARTZ	
Serial No.:	UNKNOWN	Attorney Docket No.: 41145-1001
Filed:	Herewith	Anticipated Group Art Unit: UNKNOWN
For:	INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN	

ASSOCIATE POWER OF ATTORNEY

Box: PATENT APPLICATION
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Washington, D.C. 20231

Dear Sir:

Stephen A. Slusher, a principal attorney in the above-identified application for Letters Patent, hereby appoints:

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Respectfully submitted,

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